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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
WILSON,M	
ART UNIT	**PAPER NUMBER**
1633	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Offic Action Summary	Application No. 09/369,941	Applicant(s) KENSIL, CHARLOTTE A.
	Examiner Michael Wilson	Art Unit 1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-79* is/are pending in the application.

4a) Of the above claim(s) *1-18 and 33-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-32 and 49-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's arguments filed 5-18-01, paper number 18, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. This action is non-final in view of the new rejections set forth below.

Election/Restriction

1. This application contains claims 1-18, 33-48 drawn to an invention nonelected without traverse in Paper No. 13. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 63-79 have been added. Claims 19-32 and 49-79 are under consideration in the instant application. The claims are being examined as they relate to a composition comprising an saponin, an immunostimulatory nucleic acid sequence and DNA encoding an antigen and methods of using such a composition. Claims 32 and 62 are not being examined as they relate to a composition comprising an saponin, an immunostimulatory nucleic acid sequence and antigen and methods of using such a composition which is not elected subject matter.

Sequence Rules

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The nucleic acid sequences in 28, 58, 69, 71, 78 and 79 do not have SEQ ID NOs. Claim 28 and 58 were amended on March 6, 2000 to include the SEQ ID NO; however, the SEQ ID NOs are no longer in the claims. Correction is required.** Applicant is requested to return a copy of the attached Notice to Comply with the reply. For a reply to this office action to be considered fully responsive, applicants must fully comply with the sequence rules.

Double Patenting

3. Claims 25, 26, 28, 55, 56, 58 and 76 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 65, 66, 69, 67, 68, 70 and 77, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

4. Claims 49-62, 64, 67, 68, 70, 72, 74, 76, 77 and 79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing an immune response in an individual comprising administering i) a vector comprising a nucleic acid sequence

encoding an antigen operatively linked to a promoter; and ii) a nucleic acid sequence comprising at least one unmethylated CpG to said individual such that an immune response against said antigen occurs in the individual, does not reasonably provide enablement for merely administering a saponin and a nucleic acid sequence comprising at least one unmethylated CpG without also administering a nucleic acid sequence encoding an antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are being examined as they related to a method of inducing an immune response in an individual by administering i) a vector comprising a nucleic acid sequence encoding an antigen operatively linked to a promoter; and ii) a nucleic acid sequence comprising at least one unmethylated CpG to said individual. The nucleic acid sequence comprising at least one unmethylated CpG may or may not be a part of the vector. The claims are not being examined as they relate to inducing an immune response in an individual using saponin, a nucleic acid sequence comprising at least one unmethylated CpG and an antigen.

The specification teaches that a nucleic acid sequence comprising at least one unmethylated CpG may be part of a vector that encodes an antigen (page 8, line 16). The mere administration of saponin and a nucleic acid sequence comprising at least one unmethylated CpG without a nucleic acid sequence encoding an antigen does not have a disclosed use in the specification. Claims 59-61 recite the limitation of increasing an immune response to an antigen. Administering saponin and a nucleic acid sequence comprising at least one unmethylated CpG

without a nucleic acid encoding an antigen may induce a non-specific immune response in an individual; however, a non-specific immune response against an antigen is not enabled because it does not result in any therapeutic or prophylactic effect. The specification does not teach how to use the claimed invention to induce a general immune response in an individual without a specific immune against a particular antigen. Therefore, merely administering saponin and a nucleic acid sequence comprising at least one unmethylated CpG without a nucleic acid encoding an antigen does not have an enabled use. It would require one of skill in the art at the time the invention was made undue experimentation to determine how to use a method of administering saponin and a nucleic acid sequence comprising at least one unmethylated CpG without a nucleic acid encoding an antigen such that a specific immune response against a specific antigen or pathogen was obtained in the individual.

5. Claims 19-32 and 49-62 as newly amended are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite because it is indefinite because the phrase "the nucleic acid sequence of a DNA vaccine vector" lacks antecedent basis in the claim. "...not part of a vector." may be more clear.

The phrase "immunostimulatory oligonucleotide" (claims 19 and 49) is indefinite as it relates to "the nucleic acid sequence of a DNA vaccine vector" (claims 19 and 49), the motif in claims 27 and 57, and "a nucleic acid sequence encoding the protein or peptide" (claims 32 and

62). The metes and bounds of the composition encompassed by the claims cannot be determined. The specification defines an "immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif" as an oligonucleotide that activates the immune system (page 8, line 9). The specification states the oligonucleotide may be 5-40 base pairs in length or part of a vector. However, the nucleic acid may only be 4 nucleotides in length according to claims 27 and 57. Furthermore, claims 32 and 62 state the composition may also have a nucleic acid sequence encoding an antigen or peptide. Is the nucleic acid sequence comprising a CpG motif not part of a vector? Does the nucleic acid sequence comprising a CpG motif claimed encompass any nucleic acid sequence greater than 4 nucleotides in length or 5 nucleotides in length? Can the nucleic acid sequence comprising a CpG motif also encode an antigen as long as it is not part of a vector? Can the nucleic acid sequence encoding an antigen (claims 32 and 62) have CpG motifs? What are the metes and bounds of the nucleic acid sequences comprising a CpG motif being claimed? (Claims 20-32 and 49-62 are included as they depend upon claim 19).

Claims 24 and 54 are indefinite because it is unclear whether the "dinucleotides" refers to the unmethylated CpG motifs in parent claims 19 and 49 or to some other unmethylated CpG nucleic acid sequences. E.g. it is unclear if the CpG motif in claim 19 counts as one of the CpG dinucleotides in claim 24.

Claims 32 and 62 are indefinite because the Markush group as amended is improper. Proteins and peptides are antigens. Polysaccharides, lipids, glycolipids, phospholipids and nucleic acids are not antigens.

Claims 29-31 and 59-61 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear if applicants are attempting to further limit the claims to administering a composition comprising the dinucleotide/saponin and an antigen or to administering a composition comprising the dinucleotide/saponin and increasing the immune response to an antigen that is administered to the mammal at a later time.

Claims 29-31 and 59-61 are indefinite because the phrase "when administered to a mammal", "human, or "animal" is an intended use and may not occur. If applicants intend to limit the "individual" in claims 19 and 49 to a mammal, human or animal, the claims should read "wherein the individual is a mammal", "...human" or "animal."

Claims 32 and 62 are indefinite because the Markush group "lipids, glycolipds and phospholipids" is improper. While double inclusion of an element in a Markush group may exist (MPEP 2773.05 (h)), the elements are related as genus and species. The species of glycolipids and phospholipids are completely encompassed by the genus of lipid. Therefore, the elements in the Markush group are improper.

Claims 73 and 74 are indefinite because it is unclear if the nucleic acid sequence comprising a CpG motif being claimed is 5-40 base pairs or if the immunostimulatory sequence is 5-40 base pairs and may be part of a larger nucleic acid sequence.

Claim Rejections - 35 USC § 102

6. Claims 19-21, 24, 25, 27, 29-32, 49-51, 54, 55, 57, 59-62 and claims 65, 67 and 75-77 are rejected under 35 U.S.C. 102(e) as being anticipated by Urban (Urban et al. US Patent 6,013,258, Jan 11, 2000) as supported by Krieg (Krieg et al., Tends in Microbiology, Jan. 1, 1998, Vol. 6, pages 23-26) for reasons of record.

Urban taught administering a plasmid comprising at least two unmethylated CpG nucleic acid sequence and an immunogenic HPV peptide and saponin (ISCOM) (col. 6, line 18). While not relied upon, the inherency of plasmid DNA having unmethylated CpG dinucleotides is supported by Krieg who taught that plasmid DNA is bacterial DNA that has unmethylated CpG dinucleotides (page 23, line 5; page 25, col. 1, p. 1 and 2). Saponin/Quil A is inherently derived from *Quillaja saponaria* and considered "substantially" pure because the term "substantially" is not defined in the specification and because saponin must be purified away from other compounds to be obtained. The limitation of a modified oligonucleotide (claims 25, 55, 65 and 67) is equivalent to the plasmid of Urban because the CpG sequences are part of a plasmid which has been genetically engineered. Note the "ACGC" and "ACGT" sequences within SEQ ID NO:7 (col. 14, line 6) which are equivalent to the formula in claims 27 and 57. The phrase "wherein the composition increases the immune response to an antigen when administered to a mammal", "human" or "animal" (claims 29-31) is an intended use and does not bear patentable weight in determining the structure or function of the composition being claimed because it does not necessarily occur and because it does not clearly describe the structure or alter the function of the

composition. Claims 32 and 52 are included in the rejection because it is unclear how the limitation in further limits the structure of the composition being administered (see 112/2nd) and because the nucleic acid encodes antigen. The limitation of increasing the immune response to an antigen "when administered to a mammal", "human" or "animal" (claims 59-61) is anticipated by Urban because Urban teaches administering the composition to mice and increasing the immune response to an antigen (col. 8, line 55) and because the phrase "when administered to a human" is an intended use and may not occur. All that is required is that the composition increases the immune response to any antigen. The limitation of a chemically modified saponin (claims 75-77) is equivalent to QuilA which has been added to cholesterol (col. 6, line 20). Thus, Urban anticipates the claims.

Applicants argue claim 19 as amended excludes DNA encoding an antigen and an immunostimulatory CpG nucleic acid sequence. Applicants argument is not persuasive. The specification states the CpG dinucleotide may be a part of a vector (page 8, line 16). The claims use open language and are indefinite regarding the structure of the composition being claimed (see 112/2nd). Therefore, the claims still encompass a composition comprising saponin and a plasmid comprising DNA encoding an antigen and an immunostimulatory unmethylated CpG motif.

Applicants argue that claims 65-68 require that the immunostimulatory oligo is modified which is not taught by Urban. Applicants argument is not persuasive. Claims 65 and 67 are anticipated by Urban because the immunostimulatory oligonucleotide is part of a plasmid which

has been genetically engineered. Applicants arguments as they relate to claims 66 and 68 are moot because claims 66 and 68 are not rejected under Urban.

Applicants argue that claims 75-77 are not anticipated by Urban because the saponin of Urban is not "chemically modified." Applicants argument is not persuasive. Quil A is "chemically modified" (claim 75-77) because it is combined with cholesterol which is a chemical modification.

7. Claims 19-24, 27, 29-32 and 49-54, 57, 59-62 remain rejected and claims 65, 67 and 75-77 are rejected under 35 U.S.C. 102(e) as being anticipated by Sasaki (Sasaki et al. US Patent 5,808,024, Sept. 15, 1998) as supported by (Krieg et al., Tends in Microbiology, Jan. 1, 1998, Vol. 6, pages 23-26) for reasons of record.

Sasaki taught the pBluescript II SK plasmid encoding an antigen (col. 18, lines 4-19; col. 11, lines 22-45) and combining such plasmids with QS21 (column 3, lines 36-63; see especially lines 39 and 63). pBluescript II SK inherently has at least one unmethylated CpG dinucleotide because plasmids are bacterial DNA which inherently has unmethylated CpG dinucleotides. While not relied upon, the inherency of plasmid DNA having unmethylated CpG dinucleotides is supported by Krieg who states that plasmid DNA is bacterial DNA that has unmethylated CpG dinucleotides (page 23, line 5; page 25, col. 1, p. 1 and 2). QS21 is derived from *Quillaja saponaria* and is "substantially" pure because the term "substantially" is not defined in the specification and because QS21 is a purified saponin. The phrase "wherein the composition increases the immune response to an antigen when administered to a mammal", "human" or "animal" (claims 29-31) is an intended use and does not bear patentable weight in determining the

structure or function of the composition being claimed because it does not necessarily occur and because it does not clearly describe the structure or alter the function of the composition. Claims 32 and 62 are included in the rejection because it is unclear how the limitation in further limits the structure of the composition (see 112/2nd). The limitation of increasing the immune response to an antigen "when administered to a mammal", "human" or "animal" (claims 59-61) is anticipated by Agrawal because Agrawal teaches administering the nucleic acids of the invention in combination with QS21 to humans (paragraph bridging col. 3 and 4; see col. 3, line 45) which inherently increases the immune response to an antigen as claimed.

The limitation of the CpG motif having the formula $5'X_1CGX_23'$ as claimed is equivalent to the nucleotide sequence of Fig. 6B, nucleotides 696-700 (TCGC), 794-797 (ACGC) and elsewhere, which have the equivalent formula.

Overall, Sasaki anticipates the claims because the specification states the CpG dinucleotide may be a part of a vector (page 8, line 16), because it is unclear how the phrase "the nucleic acid sequence of a DNA vaccine vector" (claim 19) correlates to the oligonucleotide (claim 19) or how the CpG "dinucleotide" (claims 24 and 54) correlate to the CpG "motif" (claims 19 and 49) (see 112/2nd) and because the claims use open language. Therefore, the claims still may encompass an immunostimulatory nucleic acid sequence comprising an unmethylated CpG motif within a plasmid.

Applicants argue claim 19 as amended excludes DNA encoding an antigen and an immunostimulatory CpG nucleic acid sequence. Applicants argument is not persuasive because

claim 19 is indefinite (see 112/2nd). The phrase "the nucleic acid sequence..." lacks antecedent basis. Therefore, the claims still encompass a composition comprising saponin and a vector comprising DNA encoding an antigen and an immunostimulatory unmethylated CpG motif.

Applicants argue that claims 65-68 require that the immunostimulatory oligo is modified. Applicants argument is not persuasive. Claims 65 and 67 are anticipated by Sasaki because the immunostimulatory oligonucleotide is part of a plasmid which has been genetically engineered. Applicants arguments as they relate to claims 66 and 68 are moot because claims 66 and 68 are not rejected under Sasaki.

Applicants argue that claims 75-77 are not ancipated by Sasaki because the saponin of Sasaki is not "chemically modified." Applicants argument is not persuasive. QS-21 is "chemically modified" (claim 75-77) because it is purified which is a chemical modification of unpurified saponin.

8. Claims 19-20, 24-27, 29-32, 49-50, 54-57, 59-62, 65-68, 73 and 74 are rejected under 35 U.S.C. 102(e) as being anticipated by Agrawal (US Patent 5,968,909, Oct. 19, 1999).

Agrawal taught a composition comprising a phosphorothoiated oligonucleotide comprising at least two unmethylated CpG nucleic acid sequences and saponin (col. 8, line 29; col. 17, line 27, SEQ ID NO:6; col. 6, line 29). Saponin is inherently derived from *Quillaja saponaria* (claims 20 and 50). Note the "TCGT" and TCGC" sequences within SEQ ID NO:6 which is equivalent to the formula in claims 27 and 57. The phrase "wherein the composition increases the immune response to an antigen when administered to a mammal", "human" or

"animal" (claims 29-31) is an intended use and does not bear patentable weight in determining the structure or function of the composition being claimed because it does not necessarily occur and because it does not clearly describe the structure or alter the function of the composition. Claims 32 and 52 are included in the rejection because it is unclear how the limitation in further limits the structure of the composition being administered (see 112/2nd) and because the composition may also comprise lipids (col. 6, line 26). The limitation of increasing the immune response to an antigen "when administered to a mammal", "human" or "animal" (claims 59-61) is anticipated by Agrawal because Agrawal teaches administering the composition to mice (col. 11, line 41) which inherently increases the immune response to an antigen as claimed and because the phrase "when administered to a mammal", "human" or "animal" is an intended use and may not occur. All that is required is that the composition increases the immune response to any antigen. Thus, Agrawal anticipates the claims.

Claim Rejections - 35 USC § 103

9. Claims 19-27, 29-32, 49-57, 59-68 and 73-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner (Weiner et al., Sept. 1997, PNAS, Vol. 94, pages 10833-10837) in view of Kensil (Kensil, 1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pages 1-55).

Weiner taught administering oligonucleotide 1643 as an adjuvant increased the humoral immune response in a mouse (page 10834, col. 1). 1643 has three unmethylated CpG motifs

(Table 1, page 10834). Note the "ACGC" "TCGA" and "TCGA" which are equivalent to the formula in claims 27 and 57. 1643 is phosphorothioated (page 10833, col. 2, 11 lines from the bottom) (claims 25, 26, 55, 56 and 65-68). Weiner does not teach combining 1643 with QS-7, -17, -18 or -21.

However, at the time of filing, Kensil taught combining QS-7, -17, -18 or -21 with other adjuvants to increase the adjuvant effect (page 6, line and page 23). QS-7, -17, -18 and -21 are purified from saponin which is purified from *Quillaja saponaria* (page 3).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotide 1643 of Weiner with QS-7, -17, -18 or -21 as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Weiner and Kensil are directed toward compositions with adjuvants that increase the humoral immune response and 2) 1643 and QS-7, -17, -18 or -21 could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the humoral immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to combine oligonucleotide 1643 and QS-7, -17, -18 or -21 to increase the humoral immune response.

Applicants have shown unexpected results with the specific combination of QS-21 and phosphorothioated oligonucleotide 1758. While QS-7, -17, -18 and -21 have equivalent adjuvant effects (Kensil, page 10, Fig. 2; page 12, Fig. 3), the adjuvant effect of oligonucleotide 1758 and

1643 varies (Weiner, page 10834, col. 2, Fig. 1). Therefore, it is not clear that the combination of 1643 and QS-7, -17, -18 or -21 would also have the same unexpected results.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

10. Claims 19-21, 24, 25, 27-32, 49-51, 54, 55, 57-62, 65, 67, 69, 60 and 73-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner (Weiner et al., Sept. 1997, PNAS, Vol. 94, pages 10833-10837) in view of Kensil (Kensil, 1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pages 1-55).

Weiner taught administering oligonucleotide 1758 as an adjuvant increased the humoral immune response in a mouse (page 10834, col. 1) which has an unmethylated CpG motifs and is equivalent to SEQ ID NO:1. 1758 is phosphorothioated (page 10833, col. 2, 11 lines from the bottom) (claims 25, 26, 55, 56 and 65-68). Weiner does not teach combining 1758 with Quil A.

However, at the time of filing, Kensil taught combining Quil A with other adjuvants to increase the adjuvant effect (page 6, line and page 23). Quil A is purified from *Quillaja saponaria,* is less purified than QS-7, 17, 18 or -21 and has less of an adjuvant effect than QS-7, 17, 18 or -21 (page 3, page 5, Fig. 1, page 11).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotide 1759 of Weiner with Quil A as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Weiner and Kensil are directed toward compositions with adjuvants that increase the immune

response and 2) 1758 and Quil A could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to combine oligonucleotide 1758 and Quil A to increase the immune response.

Applicants have shown unexpected results with the specific combination of QS-21 and phosphorothioated oligonucleotide 1758. However, the adjuvant effect of Quil A is not equivalent to the adjuvant of QS-7, -17, -18 and -21 (Kensil, page 11, paragraphs 1 and 2). Therefore, it is not clear that the combination of oligonucleotide 1758 and Quil A would have the same unexpected results.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

11. Claims 19-27, 29-57, 59-68 and 71-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chu (Chu et al., Nov. 17, 1997, J. Undue experimentation. Med., Vol. 186, pages 1623-1631) in view of Kensil (Kensil, 1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pages 1-55).

Chu taught administering oligonucleotide 1826 or 1760 as an adjuvant increased the IgG2a immune response in a mouse (page 1625, col. 2, Fig. 1A and 1D). 1826 and 1760 have unmethylated CpG motifs and 1826 is equivalent to SEQ ID NO:2. 1826 and 1760 are phosphorothioated (page 1625, col. 1, Table 1) (claims 25, 26, 55, 56 and 65-68). Chu does not teach combining 1826 or 1760 with Quil A, QS-7, -17, -18 or -21.

However, at the time of filing, Kensil taught combining Quil A, QS-7, -17, -18 or -21 with other adjuvants to increase the adjuvant effect (page 6, line and page 23). Quil A is purified from *Quillaja saponaria,* and QS-7, 17, 18 and -21 are purified from a less pure formulation of saponin.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotides 1826 or 1760 of Chu with Quil A, QS-7, 17, 18 or -21 as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Chu and Kensil are directed toward compositions with adjuvants that increase the immune response and 2) 1826 or 1760 and Quil A, QS-7, 17, 18 or -21 could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to add oligonucleotide 1826 or 1760 and Quil A, QS-7, 17, 18 or -21 to increase the IgG2a immune response.

Applicants have shown unexpected results with the specific combination of QS-21 and phosphorothioated oligonucleotide 1758. However, it is unclear whether 1826 or 1760 have an equivalent adjuvant effect because the effect of nucleic acid sequences comprising unmethylated CpG motifs varies (page 9, first full paragraph of the instant application). Therefore, it is unclear whether 1826 or 1760 have an equivalent adjuvant effect as 1758. In addition, the adjuvant effect of Quil A is not equivalent to the adjuvant of QS-7, -17, -18 and -21 (Kensil, page 11, paragraphs

1 and 2). In conclusion, it is not clear that the combination of 1826 and 1760 and Quil A, QS-7, 17, 18 or -21 would have the same unexpected results as 1758 and QS-21.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

It is noted that the limitation of a CpG motif having the formula $5'X_1CGX_2 3'$ in claims 27 and 57 cannot be adequately searched as a sequence search because the nucleic acid is so small and may be part of a plasmid which is very large. The formula has been found in the references of record, but cannot be searched alone in combination with saponin.

Claim Objections

12. Claims 19-32 and 49-62 are objected to because of the following informalities: the term "compositing" in claim 19 should be "composition". Appropriate correction is required.

Conclusion

No claim is allowed. This action is non-final.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 305-0196.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER